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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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Wayne R. Danter

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01/26/2009

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EXAMINER

RAO, DEEPAK R

ART UNIT

PAPER NUMBER

1624

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DELIVERY MODE

01/26/2009

PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b>	<b>Applicant(s)</b>	
	10/522,944	DANTER ET AL.	
	<b>Examiner</b>	<b>Art Unit</b>	
	Deepak Rao	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) ☒ Responsive to communication(s) filed on 24 October 2008.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) ☒ Claim(s) 1-8, 11-17 and 19-35 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☒ Claim(s) 1-8, 11-14, 24 and 25 is/are allowed.
- 6) ☒ Claim(s) 15-17, 19-23 and 27-34 is/are rejected.
- 7) ☒ Claim(s) 35 is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)                       | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)   | Paper No(s)/Mail Date. _____                                      |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>20081024</u> .  | 6) <input type="checkbox"/> Other: _____                          |

### **DETAILED ACTION**

This office action is in response to the amendment filed on October 24, 2008.

Claims 1-8, 11-17 and 19-35\* are pending in this application.

\***Note:** In the amendment filed October 24, 2008, claims 9-10 and 18 were listed as being 'canceled' (as indicated by the status identifier and as per the first paragraph in the "REMARKS" section), however, the claim text for each of the claim was present in the claim listing. This is not consistent with 37 CFR 1.121 (c) (4) (i), which provides that:

§ 1.121 Manner of making amendments in applications

(4) When claim text shall **not** be presented; canceling a claim.

(i) No claim text shall be presented for any claim in the claim listing with the status of "canceled"

As the applicant indicated that "Claims 9, 10 and 18 have been canceled" (see page 9 of the response), it is suggested not to present claim text for canceled claims in subsequent amendments.

#### ***Withdrawn Rejections/Objections:***

Applicant is notified that any outstanding rejection/objection that is not expressly maintained in this office action has been withdrawn or rendered moot in view of applicant's amendments and/or remarks.

#### ***The following rejections are maintained:***

Claims 15-17, 19-22 and newly added claims 27-33 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating cancers of the breast, colon, prostate, and ovary; or a method of treating melanoma or chronic myeloid

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leukemia (CML), does not reasonably provide enablement for a method of treating a tyrosine kinase-dependent cancer generally. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The reasons provided in the previous office action are incorporated here by reference.

Applicant's arguments have been fully considered but they were not deemed to be persuasive. Applicant argues that 'as amended claim 15 refers to 'a method of treating tyrosine kinase-dependent cancer' and the Declaration filed herewith shows evidence of enablement for such a method of treating cancer or tyrosine kinase-dependent cancer in conjunction with data of pages 28-29 of the specification'. Applicant's amendments and arguments along with the Declaration and the data of the specification have been fully considered. Contrary to applicant's arguments, the Declaration and/or the data of the specification does not establish enablement for the entire scope of the instant claims that are drawn to 'a method of treating tyrosine kinase-dependent cancer' which includes all types of cancers that are associated with tyrosine kinases. Applicant has not provided sufficient evidence that establishes that the disclosure would have enabled for one skilled in the art at the time of filing. It was clearly set forth in the previous office action that the instantly claimed therapeutic activity is generally unpredictable and highly structure specific area. Relevant portions from previous office action are provided below for convenience:

The testing assays provided in the specification at page 28 are related to specific cancer cells, however, there is no disclosure regarding how this data is extrapolated to the treatment of the all types of diseases and conditions encompassed by the instant claims. Applicant did not state on record or provide any guidance that the assay provided is correlated to the clinical efficacy of the treatment of various disorders of the claims. As can be seen from specification

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page 27, the activity data holds significant role in determining the dosage regimen based on the minimal effective concentration of each of the compound to achieve the desired inhibition of the kinases.

The use disclosed in the specification is as protein tyrosine kinase inhibitors, useful to treat a large list of diverse diseases, some of which are listed in page 11. Example 1 in page 28 of the specification describes the anti-cancer activity of some of the compounds in **specific cell types**, however, there is nothing in the disclosure regarding how this *in vitro* data correlates to the treatment of the diverse disorders of the instant claims. The diseases and disorders encompassed by the instant claims include various types of proliferative disorders, cancers, tumors, etc., some of which have been proven to be extremely difficult to treat. Further, there is no reasonable basis for assuming that the myriad of compounds embraced by the claims will all share the same physiological properties since they are so structurally dissimilar as to be chemically non-equivalent and there is no basis in the prior art for assuming the same. Note *In re Surrey*, 151 USPQ 724 regarding sufficiency of disclosure for a Markush group.

Further, there is no disclosure regarding how all these assorted types diseases are treated. See MPEP § 2164.03 for enablement requirements in cases directed to structure-specific arts such as the pharmaceutical art. Receptor activity is generally unpredictable and highly structure specific area, as evidenced by the wide range of results obtained for the tested compounds. It is inconceivable as to how the claimed compounds can treat the large list of diseases embraced by the claims having diverse mechanisms.

For example, the instant claims are drawn to 'treating various types of cancers' which includes treatment of all types of cancers of blood, lymphocytes, etc. A 'cancer' is anything that causes abnormal tissue growth. That can be growth by cellular proliferation more rapidly than normal, or continued growth after the stimulus that initiated the new growth has ceased, or lack (partial or complete) of structural organization and/or coordination with surrounding tissue. It can be benign or malignant. Thus, such term covers not only all cancers, but also covers precancerous conditions such as lumps, lesions, polyps, etc. No compound has ever been found to treat cancers of all types generally. Since this assertion is contrary to what is known in medicine, proof must be provided that this revolutionary assertion has merits. The existence of such a "silver bullet" is contrary to our present understanding of oncology. Cecil Textbook of Medicine states that "each specific type has unique biologic and clinical features that must be appreciated for proper diagnosis, treatment and study" (see the enclosed article, page 1004). Different types of cancers affect different organs and have different methods of growth and harm to the body. Also see *In re Buting*, 163 USPQ 689 (CCPA 1969), wherein 'evidence involving a single compound and two types of cancer, was held insufficient to establish the utility of the claims directed to disparate types of cancers'. Thus, it is beyond the skill of oncologists

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today to get an agent to be effective against cancers generally. In reference to cancer treatment using protein tyrosine kinase inhibitors, Traxler (Exp. Opin. Ther. Patents, 1997) stated that “pharmacological properties such as stability in biological media, bioavailability, metabolism or formulability are significant hurdles” see page 585, col. 2, lines 33-36.

The diagnosis of each of the disease is generally suggested by medical history and reports of endoscopy, cytology, X-ray, biopsy, etc. depending on the symptoms, signs and complications, which is essential to establish the dosage regimen for appropriate treatment or prevention. The disclosure does not provide any guidance towards the dosage regimen required to facilitate the treatment and/or inhibition of the claimed disorders, nor indicate competent technical references in the appropriate methods.

Applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use of the instant compounds. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, “the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved”. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Traxler, in a recent article (Exp. Opin. Ther. Patents, 1997) stated that “The concept of the inhibition of growth factor receptor-mediated signal transduction via inhibition of its protein tyrosine kinase is a novel, **not yet proven** clinical approach to the regulation of cell proliferation.”, see page 585, col. 1. Therefore, the state of the art provides the need of undue experimentation for the instantly claimed therapeutic benefits.

Further, applicants have neither provided nor identified in the state of the art, a single class of compounds that can treat all types of cancers in a patient. Further, one skilled in the art of medicinal therapy recognizes that there are complex interactions between individual genetic, developmental state, sex, dietary, environmental, drug, and lifestyle factors that contribute to the carcinogenic process, making it even more challenging to have a single therapeutic agent for the treatment of diverse diseases. Rigorously planned and executed clinical trials, incorporating measurement of appropriate biomarkers and pharmacodynamic endpoints are critical for selecting the optimal dose and schedule. A detailed understanding of the molecular mode of action of the specific kinase, alongside the elucidation of the molecular pathology of individual

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diseases is required to identify disease types and individual patients that may benefit most from treatment. It is also important to construct a pharmacologic audit trail linking molecular biomarkers and pharmacokinetic and pharmacodynamic parameters to receptor response endpoints. Therefore, it is maintained that applicants have not provided sufficient test assays or data to support the claimed therapeutic method commensurate in scope, as of the filing date of the application.

***The following rejections are necessitated by the amendment:***

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 26-34 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The newly added claim 26 recites the definition: “n is 0”, for which applicant did not provide any support in the specification as originally filed. Applicant did not indicate supporting evidence for the above amendment in the original disclosure. All of the reactions schemes and examples show that ‘n is 1’, see for example, pages 16-20. The instantly claimed genus

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according to claims 26-34 includes compounds of formula I wherein 'n is 0', which genus is not sufficiently described in the specification as filed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 22-23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 22-23 are dependent on claim 18 which is a canceled claim.

### ***Duplicate Claims***

Claim 35 is objected to under 37 CFR 1.75 as being a substantial duplicate of claim 11. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). Claim 35 is drawn to 'a composition comprising a compound of claim 1' which is substantially the same scope as that of claim 11. The specification (e.g., see page 6) describes 'pharmaceutical composition' comprising the compound of formula I and there is no other composition disclosed.

### ***Allowable Subject Matter***

Claims 1-8, 11-14 and 24-25 are allowed. The references of record do not teach or fairly suggest the instantly claimed compounds.



***Conclusion***

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deepak Rao whose telephone number is (571) 272-0672. The examiner can normally be reached on Monday-Friday from 8:00am to 5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson, can be reached at (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications

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may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

**/Deepak Rao/  
Primary Examiner  
Art Unit 1624**

January 26, 2009